

## Physics 4251/6250 – Fall 2019 Project List and Instructions

In this project, you will model a chosen biophysical phenomenon or system chosen from the list below. You are welcome to propose an alternative project, but it cannot be one that you are already doing in your research. A key component of all projects is mathematical modeling in, e.g., Python (ideally) or Matlab, or fitting data from simulations in NAMD. Additionally, you will have to review and cite the relevant literature (at least 15 papers), using it in part to determine the reasonableness of your results.

You will have to present the project to the class as well as in a paper to be turned in during finals week. This paper should be 8-10 pages, in a form suitable for publication, produced in L<sup>A</sup>T<sub>E</sub>X using the template provided, with sections including an Abstract, an Introduction that reviews some of the current literature, Methods, Results and Discussion, Conclusions, and References. **Each group member will write their own paper.** They can share data, figures, and references, but the text itself should not duplicated. Each person should also submit a review of their contribution and that of their partner along with their paper.

The project is worth 30% of your grade for undergraduates and 40% for graduate students. Presentations will be 30-35 minutes plus 5-10 minutes for questions in the last two weeks of the semester. **Papers are due by 5 PM on Wed. Dec. 11.**

### Project 1: DNA

You will examine the stretching of DNA in significantly greater detail than done in class. You will run molecular dynamics (MD) simulations of a DNA molecule (provided) under applied force (specifically “constant velocity” steered MD). You will test the effects of different concentrations of ions as well as determine if there is any dependence on the speed of pulling. Finally, you will fit the four mathematical models provided in Wang et al. just as done there and determine which model is best and what parameter values are produced by each.

### Project 2: Source of mutation

In a classic pairing of a biologist with a physicist, Luria and Delbrück conducted their now famous experiment on bacterial mutation rates more than 70 years ago. In it, they sought to test whether mutations conferring resistance to a virus arise randomly or are **induced** by the introduction of the virus, finding the former “Darwinian” hypothesis to be correct. In this project, you will write a program to simulate the consequences of this hypothesis, namely that random mutations occur at a fixed rate  $\alpha$  and determine the number of cells that contain the mutation, i.e., that will survive, after a specified number of divisions. Finally, you will compare this to the original data of Luria and Delbrück. Note: additional text from the textbook “Physical Models of Living Systems” by Philip Nelson will be provided.

### Project 3: Hidden steps in myosin-V

The protein myosin-V moves along actin filaments, carrying cargo throughout the cell. It has two legs, each with a foot that separately binds to actin. In the early 2000s, it wasn’t known how myosin moves

- does it walk hand-over-hand, with the domains alternating detachment and movement forward or does it “inch” forward like a worm? The conclusion of a set of fluorescence experiments in 2003 is that the former is correct - myosin-V walks! However, the data indicated steps of varying sizes, some jumping 74 nm at once and others alternating two steps that sum to 74 nm. Interesting, the distribution of waiting times between steps differs depending on the size of the steps, a completely unexpected result. In this project, you will determine why the distribution differs and discover the hidden, “invisible” step for the molecules with the fluorescent marker attached at base of one foot. Finally, you will write a simulation program to mimic walking with the marker attached at different locations on the leg and determine if you get the same distributions of waiting times. Note: additional text from the textbook “Physical Models of Living Systems” by Philip Nelson will be provided.

#### **Project 4: Membrane stretching**

Membranes behave as two-dimensional elastic materials. Here, you will build at least three atomistic membrane systems and calculate their area compressibility by measuring the relationship between surface-tension and area for multiple small ( $< 10\%$ ) expansions. Importantly, you will also determine if there are any size-dependent effects by simulating a larger version of one of the membranes.

#### **Project 5: Neural excitation**

In class we will derive the Hodgkin-Huxley model to describe quantitatively the electrical behavior of excitable cells. However, the HH model has four independent variables. Thus, a simplification was sought by FitzHugh in the 1950s, resulting in the two-variable model known as the FitzHugh-Nagumo model:

$$\dot{v} = c\left(v - \frac{v^3}{3} + w + I_{\text{ext}}\right) \quad (1)$$

$$\tau\dot{w} = -\frac{1}{c}(v - a + bw) \quad (2)$$

where  $v$  is akin to voltage,  $w$  relates to the behavior of the underlying ion channels, and  $I_{\text{ext}}$  is the injected current. Use the values  $a = 0.7$ ,  $b = 0.8$ , and  $c = 3$ , just as FitzHugh did. Here, you will need to analyze this system of equations, including but not limited to making a phase portrait and carrying out a linear stability analysis, identifying the nullclines and fixed points. Discretize the system of equations in time and effectively “simulate”, producing example trajectories in  $v, w$  space for different values of the parameter  $I_{\text{ext}}$  and initial points  $(v, w)$ . Next, add *distinct* Gaussian-distributed noise to each discretized equation and observe how the plots change. Finally, plot  $v(t)$  for different values of  $I_{\text{ext}}$  to observe threshold behavior, just as found in the full HH model.

#### **Project 6: Jarzynski’s equality and channel permeation**

AmtB is a membrane-bound protein that acts as a channel for ammonium ( $\text{NH}_4^+$ ) through the membrane. It is believed that it becomes deprotonated within the channel, transiting instead as ammonia ( $\text{NH}_3$ ). Using files provided in the tutorial “Methods for calculating potentials of mean force” found at <http://www.ks.uiuc.edu/Training/Tutorials/#freeenergymethods>, you will calculate the potential of mean force (PMF) for ammonia as a function of distance along the membrane normal using Jarzynski’s equality. Thus, you will have to carry out a number of steered MD simulations, measuring the work along the path for repeated runs. You can then compare the PMF that re-

sults with those provided in the tutorial using two other methods, Umbrella Sampling and Adaptive Biasing Forces.

### **Project 7: Protein extension**

Just as DNA can be modeled as a worm-like chain, so can proteins. In the paper “Elasticity, structure, and relaxation of extended proteins under force” by Stirnemann et al. (*PNAS*, 110:3847-4852), the authors apply the WLC model to simulated extension of the protein ubiquitin. You will repeat their work but for a smaller (more computational tractable) protein of your choosing. After choosing a protein, you’ll run simulations of the protein under different constant forces and then try to fit the WLC model to the resulting force vs. end-to-end distance data. Finally, assuming your results differ from those in the paper (such as the persistence length), you’ll examine possible sources of discrepancy.